Adalimumab for the treatment of Crohn’s disease

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Introduction: Crohn’s disease (CD) is a chronic inflammatory bowel disease characterized by a relapsing-remitting course with trans-mural inflammation of potentially any section of the digestive tract. Adalimumab (ADA) is a subcutaneously administered, recombinant, fully human, IgG1 monoclonal antibody that binds with high affinity and specificity to human TNF-alpha, thus modulating its biologic functions and its proinflammatory effects.

Aims: To review the available data on ADA in CD for biological properties, efficacy, and safety.

Methods: Electronic searches were conducted using the Pubmed and SCOPUS databases from the earliest records to April 2008. The search terms used were “adalimumab”, “anti-TNF”, “TNF-alpha”, “biologics”, “inflammatory bowel disease”, and “Crohn’s disease”. Reference lists of all relevant articles were searched for further studies.

Results: Available studies suggest that ADA has the potential to induce and maintain clinical response and remission in moderate-severe CD, both in anti-TNF-naïve patients and in subjects who lost their response and/or became intolerant to infliximab (IFX). ADA seems also effective in maintaining corticosteroid-free remission and obtaining complete fistula closure (although no specific randomized trials are available). No concomitant immunosuppressors seem to be necessary. Side effects appear similar to IFX, while site-injection reactions are frequent and specific. Data on immunogenicity and its clinical impact are uncertain.

Conclusions: ADA appears to be effective in inducing and maintain clinical remission in CD, including patients not manageable with IFX. Successive clinical practice and further on going trials will confirm a positive role for ADA as a new anti-TNF treatment in CD. The impact on clinical management or on resources should be more studied.

Keywords: Crohn’s disease, adalimumab, anti-TNF, treatment, biologics

Introduction
Crohn’s disease (CD) is a chronic inflammatory bowel disease (IBD) characterized by a relapsing-remitting course with trans-mural inflammation of potentially any section of the digestive tract, leading to various intestinal (internal and external fistulas, intestinal strictures, abdominal and perianal abscesses) and extra-intestinal manifestations (Baumgart and Sandborn 2007). Its incidence is 5 out of 100,000 people and its prevalence is estimated to be 30 to 50 out of 100,000 people in Western countries. The disease represents an important public health problem, as it tends to affect young people and have a chronic course affecting quality of life, social activities and working abilities.

While the etiology remains unknown, the understanding of the molecular mediators and mechanisms of tissue injury have greatly advanced (Ardizzone and Bianchi Porro 2005). The disease has been suggested to develop in a genetically predisposed subject due to a disregulated immune response to unknown antigens (probably environmental or infective, including endogenous microflora), resulting in continuous immune-mediated inflammation (Ardizzone and Bianchi Porro 2002; Baumgart and Carding 2007).
In the absence of a well-defined etiology, current treatment protocols are aimed at modulating, by various approaches, the complex inflammatory events leading to intestinal injury (Travis et al 2006). However, the treatments currently available cannot be considered curative and, even today, up to 70% of patients undergo surgery due to complications of the disease; moreover, an important subgroup of patients fail to show a significant benefit from conventional treatments, thus delineating the particular scenario of refractory CD and the need for novel therapeutic strategies (Cassinotti et al 2008).

Current therapeutic management of CD is usually defined as a “step-up” strategy, based on the use of drugs with a gradually increasing strength of action, according to disease extension, severity (mild, moderate or severe) and activity (induction vs maintenance therapy), disease pattern (inflammatory, penetrating-fistulizing or stricturing), response to current or prior medications, and the presence of complications (Ardizzone and Bianchi Porro 2005). Available treatments aim at inducing remission, preventing relapses, improving quality of life and addressing complications. Conventional drugs used in CD consist of aminosalicylates, corticosteroids, immunosuppressors [azathioprine (AZA), 6-mercaptopurine (6MP), methotrexate (MTX)] and immunomodulators such as antagonists of tumor necrosis factor (TNF)-alpha, ie, infliximab (IFX) and adalimumab (ADA).

The proinflammatory cytokine TNF-alpha is a key mediator of inflammation associated with CD (Breese and McDonald 1995). TNF-alpha is a homotrimeric protein that exists in both transmembrane and soluble forms, the latter resulting from proteolytic cleavage and release. Its biological activities include the induction of proinflammatory cytokines such as interleukin (IL)-1 and IL-6, activation of neutrophils, and enhancement of leukocyte migration (Papadakis and Targan 2000). Increased levels of TNF-alpha are found in diseased areas of the bowel wall, and in the blood and stools of patients with CD, compared with normal controls (Braegger et al 1992; Murch et al 1993; Reinecker et al 1993).

With the approval in 1998 of IFX, the first anti-TNF agent studied in CD, the treatment of this disease was dramatically changed. IFX provided swift relief with a long duration of benefit to a sizeable subgroup of CD whose disease was unresponsive to other medications. Since its initial approval, indications for its use have included fistulizing disease, maintenance of remission, pediatric CD and ulcerative colitis. Over the past decade, knowledge about the use and safety of IFX has expanded considerably.

IFX is an intravenously administered chimeric monoclonal antibody of the immunoglobulin (Ig) G1 subclass and comprises 75% human and 25% mouse sequences (Figure 1). The presence of this murine component provides a source of potential immunogenicity for humans. In facts, chimeric antibodies, such as IFX, can induce strong human anti-chimeric antibody (HACA) responses when administered to patients; these are referred to as antibodies to infliximab (ATI) and have been detected in 30% to 61% of patients treated with episodic IFX treatment compared with 7% to 10% of patients on scheduled IFX regimen (Baert et al 2003; Farrell et al 2003; Hanauer et al 2004). In the treatment of chronic disorders such as CD, for which large doses (or repeat dosing) of monoclonal antibodies may be required, the incidence of HACA has been associated with a shortening of the half-life of the drug in serum and a secondary loss of efficacy, in addition to potential infusion reactions, kidney damage and serum sickness.

In the attempt to reduce the immunogenic responses induced by chimeric antibodies, new approaches tried to remove all mouse-derived sequences, hence to develop fully human monoclonal antibodies. This was the case for ADA, the first fully human antibody to be approved.

First named D2E7, ADA (Humira®; Abbott Laboratories, Abbott Park, IL, USA) is a subcutaneously administered, recombinant, fully human, IgG1 monoclonal antibody that binds with high affinity and specificity to human TNF-alpha, thus modulating its biologic functions (Plosker and Lyseng-Williamson 2007).

The drug is available in a number of countries, including the US and EU countries, where it is approved for use in rheumatoid arthritis (RA), psoriatic arthritis, ankylosing spondylitis and, more recently, CD.

This review will focus on the use of ADA in patients with moderate to severe CD. Recent and emerging data from clinical trials have demonstrated the efficacy of ADA in this clinical setting and some considerations can be made at this time of its development.

**Methods**

Electronic searches were conducted using the Pubmed and SCOPUS databases from the earliest records to April 2008. The search terms used were “adalimumab”, “anti-TNF”, “TNF-alpha”, “biologics”, “inflammatory bowel disease”, and “Crohn’s disease”. Reference lists of all relevant articles were searched for further studies. Of the identified studies only articles published in the English language were selected. Relevant abstracts and other material from meetings were also included in the analysis. Studies concerning the use
Pharmacodynamics

ADA is a recombinant, fully human, IgG1 monoclonal antibody that binds specifically to TNF-alpha, but not lymphotoxin, thereby neutralizing the effect of the cytokine by blocking its interaction with p55 and p75 cell surface TNF receptors (Tracey et al 2008).

ADA was created using phage display technology resulting in an antibody with human derived heavy and light chain variable regions and human IgG1:κ constant regions. It is considered “fully human” meaning that the coding gene sequences do not contain elements cloned from other animal species.

ADA is produced in a mammalian cell expression system and is purified by a process that includes specific viral inactivation and removal steps. It consists of 1330 amino acids and has a molecular weight of approximately 148 kDa.

ADA affects biologic responses that are regulated by TNF-alpha, including changes in the concentrations of adhesion molecules responsible for leukocyte migration (eg, ELAM-1, VCAM-1, ICAM-1). In addition to neutralizing TNF-alpha, the clinical efficacy of ADA in CD also appears to involve induction of apoptosis (Shen et al 2005, 2006). ADA induced apoptosis of transmembrane TNF-positive monocyte and T cells and in a chimeric mouse model, with activation of intracellular caspases in vitro, thus reflecting an outside-to-inside signal transduction through transmembrane TNF-alpha. (Shen et al 2005, 2006; Nesbitt et al 2007; Mitoma et al 2008). The induction of apoptosis in T cells appeared to be concentration-dependent (Chaudhary et al 2006). Moreover, ADA was able to influence in vitro monocyte cytokine production (down-regulation of IL-10 and 12) (Shen et al 2005), to inhibit antigen-induced IFN-gamma production (Salifu et al 2006), to enhance the production of tissue inhibitor of metalloproteinases (TIMP)-1 (Di Sabatino et al 2007), and to increase the number and function of peripheral blood T regulatory cells (T-reg) from baseline in patients with RA (Vigna-Pérez et al 2005).

As bivalent monoclonal antibodies, each ADA molecule can bind up to two TNF-alpha molecules simultaneously, whereas a single TNF-alpha homotrimer can bind up to 3 molecules of ADA (Santora et al 2001; Scallon et al 2002). These features allow multimeric complexes to form under permissive stochiometric conditions.

An in vitro study showed that ADA, like IFX, exerts complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC) in transmembrane TNF-alpha-expressing T cells (Mitoma et al 2008). This is due to its effector IgG1 portion, and cells coated with antibody isotypes that fix complement and bind Fc receptors (such as human IgG1) can activate these responses (Furst et al 2006).

In a small substudy of a randomized trial of patients with RA, ADA treatment did not significantly alter the numbers of peripheral blood NK cells, monocytes/macrophages,
B cells or major T-cell subsets (Kavanaugh et al 2002). In addition, lymphocyte proliferation, DTH reactivity and antibody responses to pneumococcal antigen vaccination were not altered by ADA treatment, as was not diminished the capacity of patients with RA to develop protective antibody titers in response to influenza or pneumococcal vaccines (Kaine et al 2007).

**Pharmacokinetics**

In healthy volunteers who received a single dose of ADA 40 mg subcutaneously, mean values for peak serum concentration (C_{max}) and time to achieve C_{max} were 4.7 μg/mL and 131 hours (5.5 days). Absolute bioavailability after a single 40 mg subcutaneous dose of the drug was 64% (Plosker and Lyseng-Williamson 2007).

In general, the pharmacokinetic profile of ADA in patients with CD appears to be similar to that in patients with RA. Various pharmacokinetic analyses in patients with RA receiving single doses of ADA 0.25 to 10 mg/kg intravenously have shown that the volume of distribution was 4.7 to 6 L, systemic clearance was approximately 12 mL/h, and mean terminal elimination half-life was about 2 weeks (range 10–20 days) (Plosker and Lyseng-Williamson 2007).

Pharmacokinetic data on ADA are also available from 211 patients with moderate to severe CD who participated in the CLASSIC-I clinical trial (see below) (Paulson et al 2005). Patients were randomized to receive placebo or 1 of 3 subcutaneous ADA induction regimens. Serum ADA concentrations were sustained during the 4-week study period and increased in a dose-proportional manner.

In patients with CD receiving maintenance therapy with ADA 40 mg every other week, mean steady-state trough concentrations of the drug were quite 7 μg/mL at week 24 and week 56 (Granneman et al 2003).

Concurrent use of MTX reduced ADA apparent clearance by 44% after multiple dose administration in patients with RA; current data on the effects of this pharmacokinetic interaction with CD are limited to a small number of patients and are, therefore, inconclusive, although ADA clearance did not appear to be affected by concurrent immunosuppressant therapy in this patient population (Garimella et al 2006).

In RA, the presence of nonlinearity in ADA clearance has been reported (Granneman et al 2003) and analyses revealed that the apparent clearance of ADA increased in the presence of anti-ADA antibodies (see below). The combination of slow absorption rates after subcutaneous administration, slow elimination rates, and the appropriate dosing frequencies of ADA yields smooth and uniform concentration–time profiles at steady state, all being desirable qualities in the context of the “therapeutic window” paradigm (Nestorov et al 2004).

**Efficacy**

The clinical efficacy of ADA has been evaluated in 4 pivotal trials involving more than 1400 patients with moderate to severe CD. These randomized, double-blind, placebo-controlled, multicenter studies include 2 induction trials lasting 4 weeks (CLASSIC-I and GAIN) (Hanauer et al 2006; Sandborn et al 2007a) and 2 maintenance trials (CLASSIC-II and CHARM) lasting 52 and 56 weeks, respectively (Sandborn et al 2007b; Colombel et al 2007a). ADA was administered subcutaneously in all clinical trials. All included patients had moderate to severe disease, as defined by a Crohn’s Disease Activity Index (CDAI) of 220 to 450 (Best et al 1976).

Results of each of these studies, as well as data from other uncontrolled reports have shown that ADA can be effective in inducing and maintaining clinical response and remission in CD, both in anti-TNF-naïve patients and in subjects who lost their response and/or became intolerant to IFX. No specific trials were designed for fistulizing disease, but some data have been suggested by subanalyses of the aforementioned studies. Finally, all studies describe a significant improvement in quality of life, as assessed by the IBD-Questionnaire (IBD-Q) scores.

Controlled trials offer the best mean to establish clinical efficacy and to identify the most common side effects of a therapy. As well as for any CD drugs, but even more and more for those compounds where economical and safety implications are very important, the risk of an uncritical reception of positive results, however modest, should be considered. This situation has already occurred with previous compounds, including a successful drug such as IFX, although we can now benefit from a longer period of clinical knowledge and use. Firstly, it should be remembered that “statistical significance” does not always reflect “clinical significance”. Secondly, in designing a clinical efficacy protocol, the need to establish adequate therapeutic targets instead of creating any surrogates that emphasise otherwise modest results should be underlined. Although the use of response rate may be more efficient in determining drug efficacy, it does appear to be particularly susceptible to a high placebo effect; in this regard, remission rates may be a more appropriate and clinically meaningful primary endpoint. Fortunately, most of ADA trials have considered clinical remission as their primary end-point. Thirdly, it is worthwhile pointing out that CDAI, on which most randomized clinical trial of CD have
been based, is not a perfect instrument, being influenced by many confounding factors, thus not always reflecting the real correlation between symptoms and disease activity. Other rigorous activity indexes, such as mucosal healing, or other important patient-oriented parameters, such as quality of life, should be added in future, although their accuracy is much debated.

In conclusion, it is our opinion that the main targets for any therapy, to be considered indicative of some efficacy in CD, should be the induction and the maintenance of complete remission, and the prevention of adverse events in order to improve patient compliance, complication rate, and the need for surgery. Some data on ADA according to this view are already available, while others need to be added in future.

**Randomized clinical trials: induction of response and remission**

The CLASSIC 1 (CLinical Assessment of adalimumab Safety and efficacy Studied as Induction therapy in Crohn’s disease) was a phase III, placebo-controlled, dose-ranging induction trial, which included 299 patients with moderate to severe CD, naïve to anti-TNF therapy, randomized to 1 of 4 induction regimens at weeks 0 and 2 with ADA and followed through week 4 (Hanauer et al 2006).

The 4 induction regimens were: 1) ADA 40 mg at week 0 and 20 mg at week 2 (40 mg/20 mg; n = 74); 2) ADA 80 mg at week 0 and 40 mg at week 2 (80/40; n = 75); 3) ADA 160 mg at week 0 and 80 mg at week 2 (160/80; n = 76) or 4) placebo at weeks 0 and 2 (n = 74).

Concurrent therapies for CD, including 5-aminosalicylates, corticosteroids and immunosuppressors, were permitted at stable dosages.

The primary analysis involved a comparison of the two greatest dosage regimens of ADA vs placebo for the percentage of patients who achieved clinical remission at week 4. Secondary analyses included comparison between each ADA dosage group and placebo for the percentage of patients with a 70- or 100-point response. A response was defined as a CDAI score reduction of ≥70 points (70-point response) or of ≥100 points (100-point response) from week 0, while remission was defined as a CDAI score <150.

Results at week 4 (Figure 1) showed a significantly greater remission rate among patients treated with 160/80 (36%) or ADA 80/40 (24%) than among those who received placebo (12%) (p = 0.004 among the 3 groups). There was a linear dose response across the 3 ADA treatment groups at week 4 for the endpoints of remission and 100-point response, with only the highest dose group (160/80 mg) demonstrating statistical significance in the pairwise comparisons with placebo: 36% vs 12% for remission (p = 0.001) and 50% vs 25% (p = 0.002) for the 100-point response; the 70-point response was also significantly higher in the ADA recipients than placebo, both for the 160/80 mg dosage (59% vs 37%; p = 0.007) and for the 80/40 mg group (59% vs 37%; p = 0.01). The reduction of CDAI from baseline was evident as early as week 1. Clinical remission rates were not influenced by the use of concomitant immunosuppressant therapy (Table 1).

Only 11% (32/299) of the randomized patients had draining enterocutaneous or perianal fistulas at baseline and were unevenly distributed across the treatment groups. The rates of fistula improvement and remission for the ADA-treated patients and those receiving placebo were not significantly different, but the number of these patients precluded a powered analysis (Table 1).

The second induction trial, named GAIN (Gauging Adalimumab efficacy in Infl iximab Nonresponders), was a 4-week, placebo-controlled study which evaluated induction therapy with ADA in patients with moderate to severe CD who had either lost responsiveness or were intolerant to IFX (Sandborn et al 2007a).

Concurrent therapies, including stable dosages of 5-aminosalicylates, corticosteroids and immunosuppressors, were permitted. A loss of response to IFX was defined in patients with a previous initial response (as defined by the investigator) to at least 2 doses of IFX 5 mg/kg or more every 8 weeks, and who lacked improvement or had clinical worsening at least 2 weeks after receiving the last dose of IFX. Therefore, it should be noted that the definition of loss of response may not reflect the specific setting of daily clinical practice. Moreover, assessment of IFX failure in this study was retrospective rather than prospective, but a prospective assessment would have made enrollment difficult.

The primary end-point was clinical remission at week 4, while secondary endpoints included 100- and 70-point response, improvement in the number of draining fistulas at week 4 (decrease ≥50% in the number of draining fistulas at weeks 2 and 4 vs baseline) and fistula remission at week 4 (closure of all fistulas at weeks 2 and 4).

A total of 325 patients were randomized to receive ADA 160 mg at week 0 and 80 mg at week 2, or placebo at weeks 0 and 2 and followed through week 4.

At week 4, 21% (34 of 159) of patients in the ADA group compared with 7% (12 of 166) of patients in the placebo group achieved remission (p < 0.001). The difference between the 2 groups was evident at week 1 for a decrease...
of 70 points or more in the CDAI score; the rate of 70-point response at week 4 was greater in the ADA group than in the placebo group (52% vs 34%; \( p = 0.001 \)). The rates of 100-point response were also greater in the ADA group than in the placebo group at weeks 1, 2, and 4: 20% vs 12%, 37% vs 18%, and 38% vs 25%, respectively. P values were not provided.

The benefits of ADA treatment remained unchanged when the results were stratified for immunosuppressive therapy (Table 2), but not for corticosteroids, showing a clearly better response in patients receiving corticosteroids at baseline (Panes et al 2007).

Forty-five patients (14%) of treated patients had draining enterocutaneous or perianal fistulas at baseline. The rates of fistula improvement and remission at week 4 were similar for both groups: 20% of patients in the placebo group vs 15% in the ADA group for improvement and 8% vs 5%, respectively, for remission. Once again, the number of patients was too small to obtain definitive conclusions.

The GAIN and CLASSIC-I studies suggest that, although the response in some patients treated with ADA is good, a significant rate of subjects appear stably refractory to anti-TNF agents despite the shift from IFX to ADA, perhaps because of a shift to inflammatory pathways less dependent on TNF. Moreover, it should be noted that the GAIN study does not provide important information about the IFX treatment used before enrollment, for example, the dosing schedule of IFX (episodic vs regular maintenance), disease activity before IFX treatment began, at the time of response, and at the time of loss of response, and the cumulative dose of IFX before the loss of response or the development of intolerance. Lacking this information, the GAIN trial may have introduced a bias against ADA by enrolling patients who otherwise would have been primary nonresponders. On the other hand, the trial might have included patients who would have responded well to IFX if treatment had been differently managed (increasing dosage or dosage frequency or changing dosing schedule), which could introduce a bias favoring ADA (Mannon 2007).

### Table 1 Efficacy of adalimumab (ADA) from subanalysis in fistulizing disease and according to concomitant immunosuppressors in CLASSIC I for Crohn’s disease; outcome at 4 weeks (derived from Hanauer et al 2006)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo</th>
<th>ADA 40/20</th>
<th>ADA 80/40</th>
<th>ADA 160/80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterocutaneous or perianal fistula improvement</td>
<td>33%</td>
<td>75%</td>
<td>20%</td>
<td>8%</td>
</tr>
<tr>
<td>Enterocutaneous or perianal fistula remission</td>
<td>17%</td>
<td>75%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Remission in patients receiving immunosuppressors</td>
<td>9%</td>
<td>22%</td>
<td>10%</td>
<td>36%</td>
</tr>
<tr>
<td>Remission in patients not receiving immunosuppressors</td>
<td>13%</td>
<td>16%</td>
<td>30%</td>
<td>35%</td>
</tr>
</tbody>
</table>

### Table 2 Efficacy of adalimumab (ADA) 160/80 mg as induction therapy in GAIN trial for Crohn’s disease: remission in the overall population and in different subgroups of patients (derived from Sandborn et al 2007a)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adalimumab (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission</td>
<td>21</td>
<td>7</td>
</tr>
<tr>
<td>Patients with previous loss of response to IFX</td>
<td>20</td>
<td>8</td>
</tr>
<tr>
<td>Patients with previous intolerance to IFX</td>
<td>22</td>
<td>5</td>
</tr>
<tr>
<td>Patients not receiving immunosuppressors at baseline</td>
<td>21</td>
<td>7</td>
</tr>
<tr>
<td>Patients receiving immunosuppressors at baseline</td>
<td>22</td>
<td>7</td>
</tr>
<tr>
<td>Patients not receiving corticosteroids at baseline</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Patients receiving corticosteroids at baseline</td>
<td>33</td>
<td>4</td>
</tr>
</tbody>
</table>

*Abbreviation: IFX, infliximab.*
Adalimumab in Crohn's disease

of ADA maintenance therapy with placebo in patients with moderate to severe CD, including a subgroup previously treated with IFX, who responded to open-label induction with ADA 80 mg/40 mg (Colombel et al 2007a).

Concurrent therapies for CD, including stable dosages of 5-aminosalicylates, corticosteroids and immunosuppressors were permitted. Patients who had received IFX or any other anti-TNF agent more than 12 weeks before screening was enrolled provided that they did not exhibit initial nonresponse to the agent. At enrollment, 47% of patients were receiving immunosuppressors (AZA, 6MP, MTX), and 50% had previously received a TNF-antagonist.

At week 0, all eligible patients received open-label ADA 80 mg followed by a 40-mg dose at week 2. At week 4, patients were randomized to one of 2 different dosages of ADA or placebo as maintenance treatment through week 56. Also at week 4, patients were stratified by responder status (ie, whether or not they attained a decrease in CDAI of ≥70 points compared with baseline) and previous exposure to TNF antagonists. The co-primary efficacy end points were clinical remission at weeks 26 and 56 for the randomized responders (ie, those with a 70-point response at week 4). A number of secondary endpoints were considered, including 70-point and 100-point response.

Of the 854 patients who received induction therapy, 58% (499 patients) achieved a 70 points response at week 4 and were therefore randomized to receive 1 year of maintenance therapy with ADA 40 mg every other week (n = 260; 172 responders), ADA 40 mg weekly (n = 257; 157 responders), or placebo (n = 261; 160 responders) through week 56. After randomization, patients experiencing a disease flare (increase in CDAI of ≥70 points compared with week 4 and a CDAI score ≥220) or sustained non response (did not attain a CDAI decrease of ≥70 points compared with baseline) at or after week 12 were switched to open-label treatment with 40 mg ADA every other week; this dosage could be escalated to open-label treatment with 40 mg weekly for those with continued non response or recurrent flare.

Results at weeks 26 and 56 for randomized responders showed significantly greater remission rates at both time points for patients who received maintenance therapy with ADA 40 mg every other week (40% at week 26; 36% at week 56) or ADA 40 mg weekly (47% at week 26; 41% at week 56) than for patients who received placebo (17% at week 26; 12% at week 56) (p < 0.001 among the 3 groups) (Figure 2). Statistically significant (p < 0.05) differences in remission rates between the ADA and placebo treatment arms were observed by week 6 and were sustained through week 56.

Pair-wise comparisons between each active treatment group and placebo were also statistically significant (p < 0.001) for both 70-point and 100-point response at weeks 26 and 56 (Figure 2). There were no statistically significant differences between the two ADA dosages for any of these endpoints.

It should be noted that, although uncontrolled remission rates at the end of the open-label induction phase were not a primary endpoint in CHARM, which was designed and powered to evaluate the efficacy of ADA

![Figure 2](image_url)
for maintenance therapy, the induction-loading dose regimen used (80 mg/40 mg) provided similar response rates (70-point decrease in CDAI of 58%) to both the 80 mg/40 mg and 160 mg/80 mg regimens in CLASSIC I (59% for each regimen).

Among randomized responders, significantly more ADA than placebo recipients achieved corticosteroid-free remission, with a rate of patients in corticosteroid-free remission at week 26 of 35% with ADA 40 mg every other week, 30% with ADA 40 mg weekly, and 3% with placebo (p < 0.001 for pair-wise comparisons vs placebo). Similar results were reported at week 56 for these parameters, with a corticosteroid-free remission rate of 29% with ADA 40 mg every other week, 23% with ADA 40 mg weekly, and 6% with placebo (p ≤ 0.001 for ADA 40 mg every other week vs placebo; p ≤ 0.008 for ADA 40 mg weekly vs placebo).

At week 26, 30% of ADA recipients (both groups combined) had complete fistula closure compared with 13% of placebo recipients (p = 0.043), as in 33% and 13% for combined ADA groups and placebo group, respectively, at week 56 (p = 0.016). This is the main evidence currently available demonstrating any efficacy of ADA in fistulizing CD.

Subgroup analyses for randomized responders showed that clinical remission rates were greater among ADA than placebo recipients irrespective of concomitant immunosuppressive therapies (Table 3). However, rates of clinical remission at weeks 26 and 56 were numerically greater among patients naïve to anti-TNF therapy than among those who had received prior treatment with a TNF antagonist (Table 3).

The results of the CHARM trial, which had the largest sample size for a maintenance trial with ADA in CD, confirm that this drug is more effective than placebo for long-term (56-week) maintenance of remission previously obtained with an induction regimen, even at the lower dose of 80/40 mg, which is the recommended dosage in clinical practice. The CHARM study, investigating the maintenance benefit in those responding at week 4 of open-labeled adalimumab, also demonstrates some loss of response over the course of a year, although why this occurs is uncertain and may represent initial placebo responders to open-labeled treatment (Korzenik 2007).

A total of 276 patients who completed the 4-week CLASSIC-I trial entered a long-term extension study named CLASSIC-II (Sandborn et al 2007b). This was a randomized, placebo-controlled, maintenance follow-up trial, demonstrating that ADA 40 mg every other week or weekly was superior to placebo in maintaining remission for 1 year in patients with moderate to severe CD naïve to anti-TNF agents who achieved remission with ADA induction therapy.

Eligible patients (belonging to the pool of CLASSIC-I enrolled patients) were treated with ADA 40 mg at week 0 (corresponding to week 4 of CLASSIC-I) and week 2. Those in remission at both week 0 and week 4 (n = 55) were randomized to receive ADA 40 mg every other week (n = 19), ADA 40 mg weekly (n = 18), or placebo (n = 18), through 56 weeks.

At week 56, remission was maintained in 79%, 83%, and 44% of patients in the respective groups (primary endpoint), with a statistically significant difference between each ADA group and placebo (p < 0.05). The 100-point response at week 56 was also better in ADA recipients (79% vs 89% vs 56%, respectively), as was the 70-point response rates (79% vs 89% vs 72%), although differences between groups were not statistically significant.

CLASSIC-II also included an open-label arm in which patients who did not achieve remission at week 0 and

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Placebo</th>
<th>ADA 40 mg every other week</th>
<th>ADA 40 mg weekly</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week 26</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With immunosuppressors</td>
<td>16%</td>
<td>39%</td>
<td>44%</td>
</tr>
<tr>
<td>Without immunosuppressors</td>
<td>21%</td>
<td>42%</td>
<td>56%</td>
</tr>
<tr>
<td>Previous TNF-antagonist</td>
<td>16%</td>
<td>32%</td>
<td>42%</td>
</tr>
<tr>
<td>TNF-antagonist naïve</td>
<td>18%</td>
<td>47%</td>
<td>50%</td>
</tr>
<tr>
<td><strong>Week 56</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With immunosuppressors</td>
<td>12%</td>
<td>37%</td>
<td>39%</td>
</tr>
<tr>
<td>Without immunosuppressors</td>
<td>13%</td>
<td>33%</td>
<td>50%</td>
</tr>
<tr>
<td>Previous TNF-antagonist</td>
<td>10%</td>
<td>31%</td>
<td>34%</td>
</tr>
<tr>
<td>TNF-antagonist naïve</td>
<td>14%</td>
<td>42%</td>
<td>48%</td>
</tr>
</tbody>
</table>

Table 3 Remission rates stratified by immunosuppressors use and previous TNF-antagonist experience, in CHARM for Crohn’s disease (derived from Colombel et al 2007)
4 received ADA 40 mg every other week (n = 204), with dosage escalation permitted if necessary. A further 17 patients discontinued therapy at or before week 4 and were not evaluated for efficacy. At week 56, 46% of the 204 patients treated with open-label ADA were in clinical remission, 65% had a 100-point response, and 72% had a 70-point response.

The efficacy of ADA was not affected by the use or non-use of immunosuppressive agents in either the open-label cohort or the randomized cohort.

It is relevant to note that the randomized part of the study included a highly selected group of patients who had rapidly responded to the drug (remission after 4 weeks of treatment) and had also shown the ability to maintain remission with further open-label treatment during an additional period of 4 weeks before randomization. The 30 patients who achieved remission under treatment with ADA in the induction phase and were still in remission at week 56, represent 16.2% of the cohort of all patients who received active treatment during the entire study. Furthermore, these patients did not have sustained remission because corticosteroid withdrawal was mandatory in the randomized cohort, and 21% of patients treated with ADA and in remission at week 56 were receiving corticosteroids (Panes et al 2007).

**Uncontrolled studies and case reports**

In addition to the GAIN study, some smaller open label trials have been published confirming the efficacy of ADA in patients with active CD who lost responsiveness or developed intolerance to IFX (Sandborn et al 2004; Papadakis et al 2005; Anwar et al 2006; Peyrin-Biroulet et al 2006; Seiderer et al 2007; Hinojosa et al 2007; Ho et al 2008).

In the largest of these trials, Hinojosa et al (2007) analyzed the outcome of 58 patients with moderate-severe CD (36 with luminal disease and 22 with fistulizing disease; some with both disease types), who lost response or was intolerant to IFX, receiving an induction therapy with ADA 160/80 and followed up to 52 weeks. At week 4, patients with luminal disease achieved remission in 42% and 70-point clinical response in 83%. Of the 22 patients with fistulizing disease, 23% experienced fistula remission (complete closure of all fistulas that were draining at baseline), and 41% experienced fistula improvement at week 4. Longer-term results are not available for this ongoing 52-week trial.

Seiderer et al used ADA as an induction and maintenance treatment for 16 patients with CD either refractory (n = 8) or intolerant (n = 8) to IFX. Patients received ADA 160/80 mg, followed by 80 mg every other week. In 10 of 16 patients (63%), remission was induced (n = 8) or maintained (n = 2) for at least 8 weeks. In 6 of these 10 patients ongoing remission was observed for more than 24 weeks (Seiderer et al 2007).

Sandborn et al assessed the tolerability and clinical benefit of ADA in 24 patients with CD who had lost response or were intolerant to IFX, and were treated with ADA 80/40 mg and then 40 mg every other week through 12 weeks. If patients did not achieve clinical remission, the dose was increased to 40 mg weekly. Of 17 patients with baseline active moderate-severe CD clinical, remission occurred at weeks 4 and 12 in 12% and 29%, respectively, while clinical response was achieved in 41% and 59%. Importantly, 79% of patients required to increase the dose of ADA during weeks 4 to 6, thus increasing the cost of medication for the majority of patients (Sandborn et al 2004).

Papadakis et al have retrospectively reviewed 13 patients with active CD with attenuated response to IFX, who were treated with ADA over a 6-month period (Papadakis et al 2005). Induction treatment consisted of ADA 80/40 mg, followed by a maintenance regimen of 40 mg every other week. Fifty-four percent of patients had a complete response (defined as a Harvey-Bradshaw index (HBI) ≤4 and withdrawal of corticosteroid treatment); 31% had a partial response (decrease of ≥50% in HBI and tapering of corticosteroids to lower doses than used at the start of ADA treatment); and the remaining 15% were non responders. In 6 patients, the maintenance dose was increased in order to maintain clinical response: in 3 patients the dose was increased to 80 mg every 2 weeks, in 2 patients to 80 mg every week, and in 1 to 120 mg every 2 weeks. About 73% of patients on concurrent corticosteroids were able to discontinue or significantly decrease their dose of steroids. “Significant decrease” was not defined in this paper, and it would be important to know how many patients were able to completely discontinue steroids.

Peyrin-Biroulet et al (2006) evaluated, in a 52-week open-label trial, the efficacy and safety of ADA maintenance therapy in 24 CD patients who lost response to IFX (as judged by the investigator despite an increase of IFX dosage or of dosage frequency). The patients received an induction regimen of ADA 80/40 mg at week 0 and 2 respectively, and then 40 mg every other week. The primary efficacy measure was clinical remission at week 52. Clinical remission rates were higher at weeks 4 (16/24, 67%) and 52 (14/24, 58%) compared with baseline (8/24, 35%) (p = 0.043 at week 52).

Recently, Ho et al (2008) have retrospectively reviewed the efficacy and safety of ADA in the clinical setting of patients with medically refractory CD treated with ADA in Edinburgh, over a 3-year period. Twenty-two
patients with CD, refractory or intolerant to corticosteroids and immunosuppressors, were treated using an 80/40 mg induction regimen followed by fortnightly 40 mg treatment. Twenty patients were previously treated with IFX: 36% had previous infusion reactions, 27% no response, and 14% lost response to IFX. Over a period of 1 year, 68% were in clinical remission and 67% avoided further surgery for active disease. However, 59% required dose escalation to 40 mg weekly. Of note, these authors for the first time have shown that ADA can be effective in the primary non responders to IFX, although their number was very small; in fact, 3 (50%) primary non responders to IFX achieved remission.

Various other case reports and small pilot studies are also available indicating the successful and/or safe use of ADA for the treatment of CD during pregnancy (Vesga et al 2005; Coburn et al 2006; Mishkin et al 2006), in pediatric patients (Mian and Baron et al 2005; Deslandres et al 2006; Hadziselimovic 2008), and in IFX-allergic patients (Youdim et al 2004; Stallmach et al 2004; Lester et al 2005). However, ADA is generally not recommended for use during pregnancy or lactation, and its efficacy and safety have not yet been established in children.

A recent case report by Davis et al (2008) described the successful use of ADA in a 4-year-old child with CD and associated glycogen storage disease type Ib. This patient, who was refractory to conventional therapy, including G-CSF, and was intolerant to IFX, showed a complete clinical and endoscopic remission after 22 weeks of ADA treatment.

To date, no trials have examined the efficacy of ADA for patients with extraintestinal manifestations, such as arthritis or uveitis, specifically occurring in the clinical setting of CD.

**Safety**

Apart of antibody-mediated reactions, such as infusion reactions, which are not expected with subcutaneous ADA, the safety concerns with ADA should be theoretically similar to what is seen with IFX. Moreover, the tolerability to ADA in patients with CD appears to be similar to that of other conditions for which the drug is approved, such as RA, although fewer long-term data are available from randomized trial and daily clinical practice.

Firstly, no patient died for drug-related causes. In the two short-term trials (CLASSIC-I and GAIN), serious adverse events were infrequent (1%–4%) and occurred in a similar percentage of ADA and placebo recipients (Hanauer et al 2006; Sandborn et al 2007a), including infections, CD worsening, and dehydration. The remaining adverse events that were reported by at least 5% of patients were site-injection reactions, abdominal tenderness, nausea, flatulence, nasopharyngitis, pharyngitis, and headache. Infections frequency was 16% in GAIN (Sandborn et al 2007a), while in CLASSIC-I it was 10% (ADA 40 mg/20 mg), 17% (ADA 80 mg/40 mg), and 21% (ADA 160 mg/80 mg), not dissimilar from placebo (Hanauer et al 2006). Serious adverse events were infrequent and occurred at similar frequencies in the ADA and placebo groups.

During the 4-week open-label induction phase of CHARM the most common adverse events were headache (5.9%) and nausea (5.3%). Serious adverse events were infrequent (5.3%) and included one case of multiple sclerosis. Infections occurred in 15.2%, and serious infectious adverse events occurred in 1.2% during this period (Colombel et al 2007a).

Tolerability data from the double-blind maintenance phase CHARM in general revealed the incidence of adverse events was similar between ADA and placebo groups, although there was a significantly greater incidence of infections and injection-site reactions in the ADA every other week arm, and a greater incidence of headache, fatigue, urinary tract infection, and injection-site reactions in the ADA every week arm, than in placebo recipients (Colombel et al 2007a). ADA was also generally well tolerated in CLASSIC-II (Sandborn et al 2007 b) and in the uncontrolled reports. In general the most frequent side effects with ADA are injection-site reactions. In GAIN they occurred in 11% of patients (Sandborn et al 2007a); in CLASSIC-I they developed in 26% of patients in the ADA 40 mg/20 mg group, 24% in the ADA 80 mg/40 mg group, and 38% of patients in the ADA 160 mg/80 mg group, compared with 16% of placebo recipients (Hanauer et al 2006); and in CHARM the incidence was 4.2% in the ADA every other week arm and 5.8% in the ADA weekly arm (Colombel et al 2007a). Most are mild-to-moderate and diminish in frequency after the first month of treatment. Erythema, pruritus, pain, burning sensation, and swelling have been described.

Over site-injection reactions, ADA has been associated with other, rare, cutaneous side effects. A case report by Boura et al (2006) has described the occurrence, 4 hours after a second infusion of ADA for refractory RA, of a violaceous plaque, emerging as an erythematous urticarial edema and associated with systemic manifestations (chest discomfort, epigastralgia, fever 38.4 °C, rigor, fatigue, and malaise), which was successfully treated with corticosteroids and antibiotics. Skin biopsy evaluation was consistent with the
rare diagnosis of eosinophilic cellulitis (Wells’ syndrome) (Boura et al. 2006). Beuthien et al (2004) have also reported a patient with RA who developed an erythema multiforme-like skin reaction to ADA. Within a few hours of the sixth injection of ADA, this patient developed papulopustular exanthema at the injection site on the thigh, as well as on both palms and soles, followed by desquamation of the skin of these areas. ADA was discontinued, and the exanthema rapidly improved.

Antinuclear antibodies (ANA) appear to be increased in patients treated with ADA, and clinical SLE-like syndromes have been reported in RA. The syndrome is reversible on cessation of the agent as with other TNF antagonists (Schiff et al 2006). In CLASSIC-II, of 185 patients assessed for ANA, 172 were ANA-negative at baseline; among these, 33 (19%) have been found positive to ANA at week 56 or at their last visit; all of these 33 were positive to anti-dsDNA (Sandborn et al 2007b). In the comprehensive ADA clinical development programme for CD, investigators ascertained 3 cases of lupus or lupus-like syndrome with 1506 patient-years of exposure (Colombel et al 2007b). However, of note is the fact that not all these patients met accepted diagnostic criteria for the disease. Manosa et al (2008) have recently reported 2 cases of lupus induced in patients with CD treated with ADA. Both patients had been treated earlier with IFX and were negative for ANA before beginning IFX therapy. These patients became symptomatic of lupus and were ANA positive 1 and 2 years, respectively, after initiating ADA therapy. Previous exposure to IFX may, however, be a potential risk factor for developing lupus when another anti-TNF agent is prescribed. It is not known, however, when these patients became ANA positive, as it appears these measurements were not conducted during or after IFX therapy nor before ADA use. In both cases, antidsDNA measurements were negative.

In a review of 233 cases of autoimmune diseases secondary to TNF-targeted therapies (IFX, ADA and etanercept) in 226 patients, Ramos-Casals et al (2007) found ADA to be involved in 21 cases, with vasculitis in 5 cases, SLE/lupus-like syndrome in 15 cases, and interstitial lung disease in 1 case.

Because there is a concern about the mycobacterial infections for patients treated with ADA, a PPD is mandated in the labeling of this agent. In addition most clinicians will also obtain a chest radiograph before therapy. Early studies in RA done with ADA suggested a dose–response relationship with the occurrence of tuberculosis (Perez et al 2005). Patients who developed active tuberculosis were receiving higher doses than the licensed dose of 40 mg every other week. Reducing the treatment dose and screening for the presence of latent tuberculosis reduced the frequency of active tuberculosis to 1 to 2 cases in the next approximately 2500 patients, although it did not eliminate the occurrence of tuberculosis completely.

No tuberculosis occurred during the CLASSIC-I and GAIN studies (Hanauer et al 2006; Sandborn et al 2007a), but in CHARM 2 patients treated with ADA developed pulmonary tuberculosis; of note, at baseline, they were purified protein derivative-negative (PPD) and had normal findings on chest radiographs, thus eroding the predictive role of the aforementioned screening (Colombel et al 2007a).

While data are not yet definitive, Furst et al (2006) argued that there is a lower incidence of latent tuberculosis activation after ADA (at doses used in the clinic) than IFX. Because the terminal half-lives, volumes of distribution, and clearances of these 2 compounds are approximately equivalent, simple steady-state concentrations would not account for this difference. Since IFX is given intravenously and ADA is given subcutaneously, an important difference might be the difference in peak concentrations. At present, however, the specific role of pharmacokinetic differences in the activation of latent tuberculosis remains speculative.

Patients treated with anti-TNF-agents are at higher risk of opportunistic infection; cases of histoplasmosis, coccidioidomycosis, aspergillosis, nocardiosis, listeriosis, and pneumocystis, were described in patients on ADA in RA (Schiff et al 2006).

No malignancies or lymphomas were described in CD patients treated with ADA in controlled trials, but the limited follow up of all available studies precludes a correct judgment. A case of locally advanced non-small cell lung cancer was reported in the serie by Ho et al (2008), developing in a 70-year-old female high-smoker with CD colitis. This patient had been treated concurrently with oral MTX (also previously treated with IFX, parenteral MTX, and AZA) and was maintained in clinical remission with 40 mg weekly ADA therapy (92 weeks/1.7 years). However, a recent metanalysis, involving IFX and ADA combined, suggested an increase risk of lymphoproliferative diseases and malignancies in patients treated with these agents. The pooled odds ratio for malignancy was 3.3, and the rate of malignancies was significantly more common in patients treated with higher doses compared with patients who received lower doses of anti-TNF antibodies (Bongartz et al 2006).

Other rare side effects, described in RA, included medically significant cytopenias and elevated transamines, which suggest that laboratory monitoring blood counts.
and liver functions, at least intermittently, are useful (Scheinfeld 2005).

No trial has been performed to assess ADA for the treatment of congestive heart failure. However, due to the results of trials and post-marketing data with other TNF-alpha blockers, which show they can rarely worsen congestive heart failure (Kwon et al 2003), ADA should be avoided in these patients.

Both IFX and etanercept have been linked to demyelinating disease. Few data exist for ADA, but in CHARM a case of multiple sclerosis was reported in a patient treated with ADA (Colombel et al 2007a). The package insert of ADA notes the risk of neurological disease and explains that it should not be used in patients with such a disease and should be discontinued if such a disease occurs.

A comprehensive analysis of tolerability data from clinical trials with ADA, including 1506 patient-years of exposure in CD patients, showed that ADA was associated with a rate of 5.98 serious infections per 100-patient-years, including 0.2 cases of tuberculosis per 100 patient-years (Burmester et al 2006). The report, which is available only as an abstract, also showed rates of 0.07, 0.13, 0.07, and 0 per 100 patient-years for lymphomas, demyelinating disease, lupus-like syndromes, and congestive heart failure, respectively.

Finally, it should be mentioned that the needle included in the prefilled pen used for subcutaneous administration (see below) contains natural rubber (latex) which may cause allergic reactions in patients sensitive to latex.

The ongoing Adalimumab Crohn’s Safety Registry study (PYRAMID) is expected to enrol 5000 patients or more over 5 years, and should help provide additional insight into important clinical safety questions.

**Immunogenicity**

The formation of antibodies against monoclonal antibodies has been reported and this is the case for IFX, where, despite an active debate, they were associated with infusion reactions and loss of efficacy (Anderson 2005). In general, fully human monoclonal antibodies should be less immunogenic than chimeric monoclonal antibodies (Breedveld 2000) but it is difficult to compare rates because immunogenicity analyses are product-specific (Anderson 2005). However, it should be pointed out that the concept that human proteins would be non immunogenic is not necessarily true. In fact, multiple examples exist of antibody formation to fully human therapeutic proteins, as in the case of recombinant human insulin, and fully human recombinant factor VIII clotting factor (Breedveld 2000).

Limited data are available on the development of antibodies to ADA in patients with CD, while more data are provided by RA studies. They clearly demonstrate that, despite the surrounding rationale to decrease immunogenicity while reducing the murine component of the drug, anti-ADA antibodies do develop. While ATIs are directed against the murine sequences in IFX, in the case of ADA they are directed against the variable binding region of the antibody (anti-idiotype antibodies).

In a pooled analysis of the results from the ADA trials in RA (http://www.fda.gov/cder/biologics/review/adalabb123102r1p5.pdf), the rate of formation of anti-ADA antibodies was 5.5%, with lower percentages in patients treated with concomitant MTX (1% vs 12%). In CD, data from CLASSIC I reported that only 1 patient of 225 (0.04%) in the ADA 160 mg/80 mg group had a positive assay at week 2 with a subsequent negative assay at week 4 (Hanauer et al 2006); in GAIN, none of the 159 patients treated with ADA had positive results for anti-ADA antibodies at week 4 (Sandborn et al 2007a). However, the presence of interfering measurable ADA and the short duration of these studies precluded a realistic analysis. More interesting data should come from long term studies: although immunogenicity was not evaluated in CHARM (Colombel et al 2007a), the occurrence of anti-ADA antibodies was evaluated among patients with CD in the CLASSIC-II maintenance study. During the 52-week study, 2 of 54 patients (3.7%; 1 in the placebo group and 1 in the ADA every other week group) in the randomized arm and 6 of 215 patients (2.8%) in the open-label arm of the study were positive for anti-ADA antibodies. Of the 269, 84 received concomitant immunosuppressors, none of whom were positive for anti-ADA antibodies (Sandborn et al 2007b).

Until now, no correlation was found between anti-ADA and clinical efficacy and or adverse events.

**Clinical use in Crohn’s disease**

ADA is available in more than 70 countries and is approved in the US and EU for treating patients with RA, psoriatic arthritis, and ankylosing spondylitis. In CD, ADA has received both FDA and EMEA approval with the following indications: 1) for reducing the signs and symptoms and inducing and maintaining clinical remission in adults with moderately to severely active CD who have had an inadequate response to conventional therapy, and 2) for reducing the signs and symptoms and inducing clinical remission in these patients if they have also lost response or are intolerant to IFX. Therefore, ADA is the second biologic therapy approved
for the treatment of patients with moderately to severely active CD.

ADA also seems effective in maintaining corticosteroid-free remission and obtaining complete fistula closure (although no published trial has used these as primary endpoints).

ADA is administered by subcutaneous injection, as commercially available prefilled pen (HUMIRA Pen) containing 0.8 mL (40 mg) of drug.

The recommended ADA induction dose regimen for adult patients with moderate-severe CD is usually 80 mg at week 0 followed by 40 mg at week 2. In case there is a need for a more rapid response to therapy, the regimen with 160 mg at week 0 (dose can be administered as 4 injections in one day or as 2 injections per day for 2 consecutive days) and 80 mg at week 2 can be used with the awareness that the risk for adverse events is higher during induction. After induction treatment, the recommended dose is 40 mg every other week via subcutaneous injection as maintenance treatment.

For induction treatment, ADA should be given in combination with corticosteroids. ADA can be given as monotherapy in case of intolerance to corticosteroids or when continued treatment with corticosteroids is inappropriate.

The use of ADA in CD beyond 1 year has not been evaluated in controlled clinical studies.

The results from the available trials suggest that concomitant immunosuppressive therapies do not influence response. This interaction, as well as the influence of immunosuppressant medication on antibody formation, needs to be addressed further in future clinical trials.

ADA is administered subcutaneously; this can be an important resource for patients who have difficult venous access, and may avoid intravenous catheters. Self-administration may complicate the possibility to monitor the adherence to the therapy. On the other hand this route may make the patients active protagonist of own care, thus increasing compliance. Moreover, self-administration can decrease indirect costs, such as recruitment of medical practitioners or time lost from work.

A final question that requires more attention is the appropriate induction doses for ADA (160 mg/80 mg or 80 mg/40 mg). This should be taken in account when determining their influence on costs and safety. In this regard, the data of Ho et al (2008) show that nearly 60% of patients required dose escalation to 40 mg weekly within 6 months of therapy. Weekly ADA has substantial differential cost implications and this needs to be factored into the pharmacoeconomic analyses for funding or regulatory bodies of healthcare provision.

Economic analyses of ADA in CD are not available. When weighing the risks and benefits of biologic therapy for patients with IBD, physicians must account for the consequences of undertreated IBD. These include the direct costs of hospitalizations and operations for IBD, the direct costs of treatment for side effects associated with chronic, non-biologic therapies, and indirect costs associated with lost productivity or non-monetary costs such as quality-of-life decrements. It is noteworthy to highlight also that Kaplan et al (2007) recently showed that in patients who have lost response to IFX, dose escalation will yield more quality-adjusted life-years compared to switching to ADA; however, at a considerable cost, although it should be noted that in the ADA strategy, the drug was initiated with a 160 mg injection followed by an 80 mg dose 2 weeks later with subsequent maintenance of 40 mg every other week, thus further increasing the costs.

ADA will compete with IFX at this stage in treatment.

Currently, head-to-head comparisons among anti-TNF agents do not exist, in part because of the large sample size required to demonstrate either differences between, or equivalence of, treatments. In the absence of these data, claims that one drug is better than the others have been met with scepticism by practising physicians. Comparative costs will depend on local procedures for use of TNF-alpha inhibitors.

The clinical setting of use for ADA, and its efficacy, appears to be similar to that of IFX, with some advantages, but some unanswered questions remain that will need to be addressed. Randomized clinical trials have shown that ADA can induce and maintain clinical remission in patients with moderately to severely active CD, both IFX-naïve and secondarily refractory or intolerant to IFX. The current availability of multiple TNF-neutralizing antibodies is highly desirable. As all the currently available TNF-neutralizing antibodies are immunologically unique, patients who start failing to respond to treatment with one of these biologics can be switched to one of the others, greatly enhancing clinical care (Peppelenbosch 2007).

The obvious advantage of ADA compared to IFX is the route of administration – subcutaneous, which will allow patients to self-administer this medication. This less intrusive method of drug delivery will be very much appreciated by most patients. The safety and tolerability of ADA should be similar to that of IFX in most possible side effects, but more long-term data are needed. Immunogenicity is another field that requires more studies about the frequency, risk factors
for development, and impact of antibody formation against ADA in patients with CD.

Although certain details about the optimal way to use ADA for the management of CD exist, undoubtedly this subcutaneously administered anti-TNF medication will play a crucial role in treating patients with CD (Bressler 2007).

Disclosures
None of the authors have conflicts of interest to disclose.

References


